THE AMERICAN
JOURNAL OF PHARMACY

MARCH, 1902.

THE EVOLUTION AND USE OF THE ANIMAL DIGESTIVE FERMENTS IN MEDICINE.

By Benjamin T. Fairchild.

(*Concluded from page 67.*)

The period covering the past twenty years has been one of quickened and extended interest and progress in the applied science of the digestive ferments. In this time we see the beginning of their practical use in the artificial digestion of foods for the sick by methods available in the household by means of various special preparations of the pancreas ferments. The animal digestive juices and ferments are now largely utilized in the technical laboratory in the production of peptonized foods in an agreeable, adequately nutritious and stable form, especially adapted as widely available foods for the sick. The observations of Roberts on the pancreatic ferments as peptonizing agents, led thus to a realization and development of their remarkable availability in the feeding of the sick. The dependence of pepsin upon an acid reaction, and the limitation of its action to proteids only, has restricted its use in the artificial digestion of food purely to laboratory methods. Pancreatic preparations in both dry and fluid form, prepared by direct extraction from the glands or by precipitation with strong alcohol from infusions of the gland, have come into very general use as therapeutic agents.

The manufacture of pepsin has been greatly improved, and its standard of value raised to an adequate point. The milk-curdling

enzyme has now become much employed in therapeutics as a means of administering soluble metallic salts (such as mercurials, iodides, etc.), bound up with the curd of milk or junket; also used in the preparation of whey, presenting the soluble constituents of milk—non-coagulable proteids, salts and sugar—in a fluid form as a food for the sick and in infant-feeding.

The topical application of the gastric juice so convincingly presented at the very outset of its investigation, after long escaping notice, has been brought to renewed attention and use by means of artificial gastric juice prepared directly from the fresh stomach. This interesting and important therapeutic utilization is based upon the well demonstrated facts of the solvent action of the gastric juice and its bactericidal, healing and deodorizing properties.

Trypsin is also now employed in the treatment of pus cases, especially where the indications are for the application of a solvent of a neutral or alkaline reaction. The proteolytic ferment of the pancreas is now utilized in the qualitative conversion and quantitative adjustment of cow's milk to normal human milk in digestibility and in the ratio and content of nutritive constituents.

The many products and uses of the peptic and pancreatic ferments thus brought into medicine cannot be considered here in detail. In addition to the directions already mentioned, they are utilized as therapeutic agents to promote the efficiency and toleration of medicinal agents, especially those which directly disturb digestion and circulation; as aids to digestion in acute and chronic diseases, and in various forms of dyspepsia.

From our present knowledge and view of the enzymes of the animal digestive secretions we know that the proteolytic enzymes do not exist pre-formed in the secreting cell; it may be said that they exist as "zymogens." It is uncertain as to whether there is also a zymogen of the starch-converting and curdling and emulsifying ferments. In the writer's opinion, the preponderance of evidence at the present time is that this has not been established for other than the proteolytic enzymes.

In their chemical constitution, the enzymes are presumably identical, being proteid, or closely akin to proteid in their nature and behavior. As we have already seen, some of the most recent investigators have declared their belief that they are of the nature of nucleoproteids. Whilst we have the statement long ago made by Brücke

and recently by Oppenheimer that a proteolytic ferment possessing the power to dissolve fibrin, but failing to give the proteid reactions had been isolated, it is very singular that others have not verified this, especially when we consider the careful attention the subject has received from the most eminent physiologists and chemists.

The enzymes are all soluble, destroyed when in solution, by heat; resistant to high temperature (100° C.) when in a dry form, and, with probably one or two exceptions, non-diffusible.

If we prepare an infusion of the peptic gland and submit this to heat under the physiological conditions necessary to convert into peptone all the associated proteids digestible by the enzyme, and remove these by dialysis, we shall still find this infusion to contain a non-dialysable body, exerting peptic action, precipitable upon boiling. This precipitate, so obtained, washed and submitted to pepsin-hydrochloric acid digestion, proves absolutely refractory to pepsin action. This substance has the properties of a proteid and contains nucleic acid. Identical results are likewise obtained with the pancreas enzymes.

Whether the enzymes then are nucleo-proteids, or whether nuclein may be the "material substratum" of the enzymes, cannot at present be stated. We have not obtained an enzyme in any form as yet which is not in its constitution and character analogous to proteid.

The gastric juice is generally held to contain two distinct enzymes, although some writers have recently suggested that both the curdling and proteolytic action are manifestations of the one enzyme under different conditions. This seems very doubtful from our own observations, and is without analogy in the behavior and functions of the ferments in general. Whilst pepsin is present in the stomach of all ruminant and carnivorous animals, we, however, regard the milk-curdling ferment as particularly a constituent of the nursling animal; for we have observed that in the calf and other animals the curdling activity steadily diminishes in direct ratio to the growth of the animal.

The enzyme becomes potential or vitalized only at the moment of its discharge or extrusion from the cell. Pepsinogen is not bound up with the acid, for the enzyme may be freed from hydrochloric acid without destroying its vitality; nevertheless, there is a strong chemical and physiological tie between them.

The hydrochloric acid of the gastric juice we know does not exist as free acid, but is in some way bound up to the proteids, this acid again uniting with the proteids and bases of foods and displacing organic acids. So that we must be mindful of the distinction existing between the acid of pure gastric juice and the acid contents of the digesting mass.

Seeing that the gastric juice is essentially an acid-pepsin secretion, it might be, and indeed it generally has been presumed, that solutions containing hydrochloric acid of the percentage of gastric juice would constitute favorable vehicles for the peptic ferment, as pharmaceutical products. But a mixture of pepsin, hydrochloric acid and water has not the stability of gastric juice; it differs therefrom in important particulars—in the absence of proteids associated with pepsin and united with the acid, and in the absence of inorganic constituents of the gastric juice; and we must consider gastric juice in its entity as being of a peculiar composition, essential and indispensable to the complete exhibition of its function.

Pepsin in solution with hydrochloric acid of the percentage of normal gastric juice, if brought in contact with albumen, digests it with facility, but here a portion of the acid is immediately united with the albumen and with the alkali of the albumen. If, however, we submit pepsin to long-continued contact simply in this dilute hydrochloric acid we find the pepsin to progressively deteriorate in activity. Therefore, acid cannot with impunity be added to pepsin in solution in the manufacture of products necessarily to be submitted to conditions of commerce.

The pancreas gland contains four distinct ferments. Its proteolytic enzyme is probably not elaborated in an active form, but becomes endowed with vitality by contact of the pancreas juice with the acids of the chyme, which are undoubtedly organic in a very considerable degree, and are known to be powerful developers of the latent energy or vitality of the pancreas trypsinogen.

The diastasic ferment undoubtedly exists pre-formed, and we know of no reason to assume that it requires to be developed, nor of any chemical or physiological data which would indicate this view.

The fat-digesting ferment varies greatly in the glands of different animals, and its action upon fat in reducing fat globules to a minute form is difficult to account for, especially as the ferment is not in

any known way related to an acid or an alkali; and inasmuch as alkalies themselves emulsify fats, it is difficult to differentiate between the action of the ferment and the alkali in any conditions in which both are present.

From our observations we are strongly inclined to the view that fats in contact with weak acids are more readily emulsified than pure fats; that the pancreas ferment has the power of splitting up fats is certainly undoubted.

During the normal conditions of digestion it would seem that the distribution of fat in a finely divided state is brought about (both by chemical and physiological means) through the natural commingling of the mass, the diffusion of the fats by heat, and the effect both of the bile and pancreatic secretions upon the fat as so contained in the acidulous chyme.

The milk-curdling ferment of the pancreas appears to be in every way analogous in its action to that of the rennet; in practical operations, however, it is difficult to utilize it like the rennet ferment, or to separate it for study. The clot of milk, as originally formed by the pancreas juice, is absolutely identical in apparent character with that of the rennet coagulum, but after a short time the caseine and other milk proteids are rapidly attacked by the trypsin of the pancreas juice and gradually reduced to solution, which phenomenon does not occur in contact, however prolonged, of milk with the rennet ferment, for here the coagulum gradually separates in a mass from the milk serum. The pancreas enzymes are secreted in a juice which is exceedingly complex in nature, being rich in saline constituents (in ash) and also in organic matters, those which constitute the enzymic and related bodies.

Whilst the pancreatic juice is said by many observers to be an alkaline fluid, we invariably find that infusions from the gland, prepared immediately upon being taken from the animal, or in the ordinary methods of procedure, give a distinctly acid reaction (with no alkaline reaction) due, we believe, to acid phosphates, which yield an acid ash. The fresh gland itself invariably gives an acid reaction to test paper, and I am unable to account for this except upon the hypothesis that the *juice* becomes alkaline either at the time of exudation from the gland or by some changes set up by the media with which it thus comes in contact. It is known that these ferments are not in the least degree dependent upon an alkaline reac-

tion—have no relation to an alkali in any way analogous to that between pepsin and hydrochloric acid. It cannot be too strongly pointed out that free alkali does not present a favorable medium for the extraction or preservation of the pancreas ferments in any form suitable for pharmaceutical uses. On the contrary, in alkaline solutions, the pancreas ferments all undergo rapid deterioration when submitted to the ordinary conditions of commerce. The pancreatic enzymes are so active in neutral or faintly acid media that the intervention of a feeble alkali, whilst it increases their action, does not (in the most favorable percentage) by any means do so to any great extent; and, as a matter of fact, the pancreas ferments are all readily utilizable for all purposes of artificial digestion without the intervention of any alkali whatever. In fact, with alkaline solutions the pancreas ferments are more readily destroyed than is pepsin in free acid.

It should here be mentioned that the use of an alkali in the ordinary peptonizing processes with pancreas extract is not so much to increase the activity of the ferment, as it is for its convenience in enabling us to raise the temperature of the milk to the boiling point at any time during the partial digestion of the caseine, without coagulating the partially converted caseine, for caseine acquires the remarkable characteristic of curdling upon boiling, after it has been acted upon by the trypsin; this coagulation, occurring only at the boiling point, is quite distinct from the milk-curdling reaction, the ferment having been destroyed before this reaction is reached.

As for the practical side of the zymogen subject, it need only be said that in operations with the pancreas glands, especially when we seek to utilize the proteolytic ferment, the glands are best preserved at ordinary-room temperature, according to the season, for a sufficient length of time to develop the ferment, taking care to maintain aseptic conditions. On the other hand, if the starch-converting ferment is desired, the pancreas gland may be immediately put into operation.

When we see that the latent zymogen becomes the potential enzyme when in contact with the food in normal digestion, and when existing in the gland is not utilizable unless likewise vitalized and developed by appropriate means out of the body, we are at a loss to attribute any virtue to the "mother" ferment in medicine; for the very evident reason that as a mother ferment it is valueless, and becomes valuable only when it loses the characteristics of a zymogen and becomes an "enzyme."

The behavior of the various digestive juices toward each other, their related rôle in the digestion process, has been the subject of immense research, theory and conjecture, and opinions of the widest possible variance have been expressed. This variance can be accounted for in a great degree by the nature and oftentimes inconclusive methods of experiment; the fact is sometimes lost sight of, that the contact of these enzymes in solution and in various media, acid, neutral or alkaline, introduces conditions foreign to those met with in the alimentary tract.

The first and only positive conclusion to be drawn from such experiments is, that solutions of mixed ferments which are found to exert injurious effect upon each other, under the ordinary conditions to which they must be submitted in use, should not be prepared and presented as pharmaceutical products.

We have particularly noted that the behavior of free hydrochloric acid towards the ferments is distinct from that of the gastric juice itself where the acid exists in peculiar physiological relation to the various proteids. This is the common observation of physiologists. Free hydrochloric acid behaves, for instance, very differently to starch digestion (of any diastase) from the equivalent amount of acid as combined in the gastric juice.

The fact that diastase is injured in solution by maceration with pepsin and hydrochloric acid does not make it by any means conclusive that the saliva is useless in the stomach; for it must be considered that the various juices from the salivary, gastric, and pancreatic glands are secreted under the stimulus of food, are brought together mingled with foods of a complex nature and in various stages of digestive conversion; and that the various constituents of the juices and of the foods have important functions in the whole digestive scheme. Furthermore, there are various stages of activity and reactions of media in the normal progress of digestion.

In the therapeutic use of the digestive ferments we are by no means dealing with normal digestion, nor are we restricted solely to one period or one method in the introduction of the various enzymic agents into the economy. This subject is of very great importance as regards the therapeutic use of the digestive ferments.

The writer dealt with this subject in a pamphlet on the "Extract of the Pancreas and its Uses," in 1883, and referred to his experiments

made with the gastric juice obtained by permanent fistula in a perfectly healthy dog, and the use of this fresh juice in digestion experiments upon foods in association with the pancreas ferments. Later, in his "Handbook of the Digestive Ferments," 1892, he especially called attention to the distinction between pharmaceutical compatibilities of the enzymes and their physiological relations and therapeutic adaptability.

In our review of this subject, we are struck with the fact, as in the history of all science, that there are periods of productiveness, of sterility, of reaction; that observations of the greatest importance and significance are unheeded or oftentimes directly denied, or become the subject of controversy when it would seem that they could have been corroborated by the simple repetition of the experiment; and thus we see the evolution of errors, and indeed the survival of error.

Investigators make correct and important observations on the special phenomena investigated, yet propound theories radically erroneous, not really deducible, and beyond the scope of the facts elicited. They come close to the heart of the matter, yet either discontinue, or, by faulty hypotheses, are diverted from the direction which should have led to great discoveries.

Errors concerning the nature, behavior, and relations of the enzymes have led to the preparation and employment of incompatible compounds, and have operated greatly to retard their utilization and the wide clinical investigation which would fully make known their therapeutic possibilities.

The early idea that pepsin should preferably be exhibited in small doses, the prevalence of mere saccharated attenuants of pepsin, led to a state of things which naturally was not favorable to any adequate development of its possibilities as a therapeutic agent.

As for "pancreatine," the erroneous impression early conceived (and perpetuated by constant repetition of the statement) that the pancreas ferments could only act in an alkaline media, bore a relation to alkalies analogous to that of pepsin to acid, has created a false presumption as to their therapeutic limitations.

In pharmacy we have yet to completely recognize that the enzymes have limitations and susceptibilities and compatibilities of a radically different nature to those of drugs and chemicals. For even at the present time we see that the enzymes are sometimes

destroyed when prepared with the best of purpose; and this in a way which does not at all exist as regards chemical preparations, simply from the universally recognized facts as to the compatibility and reactions of chemicals. It will be interesting to mention a few instances for their present practical importance:

It happened that Scheffer's interest in the subject was co-existent with the "elixir" mania, when the tendency was to produce as many combinations as possible, rather than to ascertain those most eligible for this form of exhibition. Naturally, pepsin and pancreatine did not escape.

Scheffer insisted on the incompatibility of bismuth in solution with pepsin. The writer has without success endeavored to prepare a solution which should retain pepsin in a vital form in contact with bismuth in solution for a sufficient length of time to justify its issuance as a pharmaceutical product. Compounds of pepsin and bismuth in solution are yet in commerce, and have a place in formularies.

That the ferments combined in solution are antagonistic to each other has often been pointed out. Scheffer early called attention to the incompatibility of pepsin and pancreatine, and pepsin and diastase in elixirs. It is impossible to prepare any media suitable for the preparation of the enzymes of the stomach and pancreas in combination in solution; for whether the reaction of the preparation be neutral, alkaline, or acid, there will be a gradual, sure, progressive deterioration of the product under the commercial conditions to which the preparation must be submitted. If the liquid preparation of the mixed peptic and pancreatic ferments be neutral or alkaline, the pepsin becomes destroyed; if acid, all but the pepsin perish, and the acid compound will therefore be found to be devoid of any pancreatic activity—capacity to convert starch, or to convert proteids in neutral or alkaline media.

On the other hand, it is a fact that suitable solutions of peptic and pancreatic ferments can be mixed extemporaneously and found to retain the virtues of the component ferments for a sufficient length of time for their use in the ordinary method of prescribing.

The rôle of hydrochloric acid, since Schwann's time (both its normal function and the limitations of its compatible percentage) has become thoroughly known; yet free mineral acids in destructive degree to the enzymes are often used in pharmaceutical prepara-

tions. And it has been even possible now for the assertion to receive publication that hydrochloric acid is the real digestant of albumen in the pepsin test.

Alcohol and glycerin in relation to the ferments are so important that they should receive attention.

In order to preserve the enzymes in solution, some antiseptic must be employed, and alcohol and glycerin prove the most desirable for pharmaceutical preparations of the enzymes, as they are in galenical preparations in general. The value of glycerin in the extraction and preservation of the enzymes is well known; we would say, however, that we cannot regard concentrated glycerin as being favorable for direct gland extraction; dilution with water is advantageous.

A great deal of misconception has existed regarding the relation of alcohol to the digestive ferments, especially as to the pharmaceutical and therapeutic significance of the facts, that strong alcohol precipitates pepsin; that pepsin does not digest well in the presence of diluted alcohol.

The writer, in his "Hand-Book of the Digestive Ferments," published in 1892, pointed out that alcohol retarded digestion *in vitro* simply for the reason that alcohol is not a media either for the activity of pepsin or for the solution of the products of digestion; that water is the physiological media in which the ferment performs its functions and by which the products of digestion are taken up as they are formed. And in his experiments with the influence of various agents upon digestion, he showed that glycerin, peptone, sugar, and other substances, likewise retarded digestion, not because they exerted in themselves any injurious influence whatever upon the ferments, but simply in the degree to which they diminished the proportion of water and its consequent capacity as a media.

The products of digestion all clog the action of the enzyme by which they are formed simply to the degree to which the media becomes saturated with them, not because they "paralyze" or injure the ferment. For upon the removal of these products by dialysis, and the addition of a fresh quantity of albumen, or by the addition of a fresh volume of the acidulated water and the addition of albumen, the ferment will exhibit its digestive action; and repeatedly, to such an extent that we do not really know the limits of its action —the life of the enzyme.

Alcohol in any percentage used in pharmaceutical and medicinal preparations is immediately diluted to a negligible quantity in the stomach in its relation to the enzyme in its ordinary exhibition; and in submitting alcohol preparations to the usual digestive test the alcohol forms so small a percentage of the digesting mass as to exert no retarding influence upon the action of the enzyme.

It was thought that because wines of pepsin were found by Squibb to be feeble or practically inert, their defect was necessarily due to the presence of alcohol; but this is not the fact.

In the first place, there was no certainty that the vinous or elixir preparations of pepsin had ever had any vital pepsin in them, or that the pepsin had not been injured by the acid in the preparation.

The conventional quantity of pepsin used in those days was a grain of the saccharated to one or two teaspoonfuls, so that a teaspoonful of such preparation could by assay digest only twelve to fifteen grains of albumen. Preparations containing sufficient alcohol and glycerin to ensure stability are readily made directly from the stomach, of which one teaspoonful upon U.S.P. assay will convert from 2,000 to 3,000 grains. There is an evident error in the attempt sometimes made to "assay" fluid preparations of pepsin containing alcohol by adding the coagulated albumen directly to the preparation. The question to be asked of an alcoholic preparation of pepsin is, whether it exhibits the action of pepsin when submitted to the proper (physiological) conditions—just as we assay the dry ferment, and thus only we determine its pepsin strength.

It was early observed that pepsin was destroyed by maceration with sodium carbonate and free alkali in minute percentages; pepsin has also been spoken of as being "altered" or "modified" by the action of an alkali.

Inasmuch as formulas have been suggested in which the neutralization of the acid pepsin infusion is directed, it is worth while to mention that pepsin is injured if the neutralization be carried to the very faintest alkalinity, and that this occurs instantly, and at ordinary temperatures; the pepsin cannot be considered "modified" or "altered" pepsin in any sense; it is simply annihilated; its activity cannot be restored by acidification or by any treatment.

In a word, it may be said that in determining the pharmaceutical possibilities of a preparation of the enzymes, the question is not

first (or necessarily at all) to be considered as to whether it is a "clear," visibly compatible preparation; its value can only be ascertained by submitting it to actual assay; that is to say, a fluid preparation must be tested by precisely the same means as the dry ferments. The preparation, then, should have such stability as to reasonably ensure its coming into medicinal or technical use in a proper form, assuming, always, that it will receive a proper degree of care in consideration of its organic nature; that it will not be exposed to heat, and that a proper rotation of supply will be observed.

The therapeutic use of the digestive enzymes in the peptonization of food is based upon purely physiological grounds, differing from ordinary alimentation only in the degree and extent to which the food is pre-fitted for assimilation when exhibited.

The chemico-physiological investigations as to the physiological reaction of the proteids, their cleavage products and derivatives, when introduced into the system otherwise than by the gastro-intestinal tract, interesting and practical as they are in advancing the domain of our knowledge, so far throw no light on the normal or abnormal processes in the body, and have presented no ground in the mind of any investigator, we believe, for any conclusions or theories, of significance in practical medicine. Especially unfounded, for instance, is any assumption that the more soluble proteids of digestion may be considered less valuable than the native or partially converted proteids.

We know well the composition and value of the native food, and the nature and object of the digestive conversion. Wide experience has well determined that a normal dietary must contain the varied elements of food, and in proper nutritive balance, and that the most minute elements thereof, even the inorganic, exert a marked influence upon the acceptability and digestibility of the foods with which they are associated.

The solution of food is essential to its availability for nutrition, and by means of the animal enzymes it became for the first time possible to prepare fluid food actually containing the entire digestible solid in solution in a non-coagulable form, thus utilizing in the feeding of the sick the normal typical foods, farinaceous and proteid.

The instinctive repugnance to solid food in disease has in itself led to the evolution of diet in therapeutics, and the peptonized foods

have naturally been a scientific and practical advance in contrast to the reliance upon fluids containing little or no solids, or solids in an indigestible form.

The disastrous effects in the past of delusive ideas as to what constituted food for the sick have been seen in the dependence so largely placed upon beef tea and extracts containing purely stimulating nitrogenous bodies. The effect produced upon animals in feeding them upon pure gelatin, or protein, or sugar, only confirms experience and reason as to the futility of such experiments in determining the value of foods, for if we were to measure the value of food elements by such results, we should logically have to conclude that no element is suitable for nutrition.

It is here interesting to mention that we are now obliged to qualify the view once so generally accepted as to the absolutely innutritive quality of gelatin. Recent physiological investigations go to show that gelatin in the ordinary diet exerts a marked influence in conserving and promoting the energy of other protein compounds, and probably in the building up or the replacing of the connective tissues analogous to gelatin.

At the outset of this paper the writer referred to the far-reaching scope of the subject. It will be seen that from whatever direction we approach the physiological and pharmacological investigations involved, we find matter of scientific and practical interest, and embodied in voluminous literature. Reference even to these researches has only been possible by restricting ourselves to those points of the greatest practical purport.

It is evident that we have arrived at a position where we can deal with the enzymes in pharmacy and medicine with as much practical certainty as with drugs and chemicals. It is true that we do not know what pepsin is: but if we ever succeed in isolating the enzymes, in order to prove for them a peculiar chemical constitution, it is not easy to see how we shall thereby make advance in pharmacy or medicine. Inasmuch as we do not know the chemical constitution of the enzymes; have no chemical tests or reagents to distinguish them as a group or as individuals, or, as it is often expressed, "we know the digestive ferments only by their action," this is often interpreted or stated from the viewpoint of presenting a distinct limitation and defect in our knowledge. But the physiological test quite transcends in delicacy the chemical, for it enables us to get the char-

acteristic action of the ferment from an amount so small as to quite elude and defy analysis. Just as in the anti-toxins, the characteristic effect is obtained from an amount so small as to even tax the imagination.

It may be said, also, that we do not know why sodium chloride exerts an unfavorable influence upon the proteolytic enzyme *in vitro*, but it positively does, even when present to the extent of 0·2 per cent. Likewise, we do not know why some of the extractive matters present in the pancreas secretions and in saliva (and in malt also) exert a profound influence upon the starch-covering ferment. We however know that inorganic salts in association with the ferments in normal juices exert a powerful action, and upon the separated enzymes themselves, and are in some way intimately related to their life and activity. We know how to extract the enzymes and preserve them, and how to apply them in many important directions; know their compatibilities and incompatibilities; and we are also able to distinguish differences between simple solutions of the ferments and the secretions of the glands themselves.

The limitations of our knowledge, whilst presenting most inviting subjects of inquiry, are mainly in their biological relations. The whole field of investigations in relation to the therapeutic utilization of the animal gland secretions is the object of active laboratory and clinical study, and we may naturally anticipate yet further additions to the brilliant achievements already made.

BIBLIOGRAPHY CHRONOLOGICALLY ARRANGED.

Reaumur: Mem. de l'Acad. de Sciences, 1752, p. 266, 461.

Stevens: Inaug. Thesis University of Edinburgh, 1777 (De alimentorum concoctione).

Hunter, J.: Philos. Transactions, 1772.

Spallanzani: Experiences sur la Digestion de l'Homme, etc., par Jean Senebier. Geneve, 1783.

Leuchs: Kastner's Arch. f. d. ges. Naturlehre, 1831.

Beaumont: Experiments and Observations on the Gastric Juice, 1834.

Eberle: Physiologie der Verdauung, 1834 (reprint 1838).

Müller, J.: Physiologie, 2d ed., 1835.

Müller and Schwann: Müller's Arch. f. Anat., 1836.

Schwann: Müller's Arch. f. Anat., 1836.

Wasmann: Inaug. Dissert, Berlin, 1839.

Burdach: Physiologie, French transl., 1841, with notes by the younger Burdach.

Lehmann: Lehrb. der physiol. Chemie, 1842 (1st ed.).

Blondlot: Traite analytique de la digestion. 1843.

Bouchardat et Sandras: Acad. de Sciences, 1842.

Bernard: Comptes rend. Acad. de Sciences. 1845, p. 88.

Frerichs: Article "Verdauung" Handwörterbuch f. Physiologie, by Wagner, 1846.

Miahle: According to Meissner, 1845.

Lehmann: According to Meissner, 1850.

Bernard: Arch. de med., etc., 1849.

Bidder and Schmidt: Die Verdauung.

Corvisart: Sur une fonction peu connue du pancreas, etc., Paris, 1857–8.

Beale: Archives de Medicine, 1858.

Meissner: Zeitsche f. rat. Med., 1859, Vol. VII, VIII.

Brücke: Sitzungsber. d. Wiener Akad., 1859, XXXVII.

Danilewsky: Virchow's Arch., 1862, No. 25.

Krasilinikow: (cited by Hammersten) 1864.

Kuehne: Virchow's Arch., 1867, No. 39.

Von Wittich: Pflüger's Arch. d. Physiol., 11, 1869.

Scheffer: AMER. JOURN. PHARM., 1872.

Ebstein and Grützner: Pflüger's Arch. d. Physiol., 1873.

Pavy: Treatise on Food and Dietetics, 1874.

Klemensiewicz: Sitzunsber. d. Akad. d. Wiss., 1875, LXXL.

Heidenhain: Pflüger's Arch. d. Physiol., 1875.

Scheffer: Proceedings Amer. Pharm. Ass'n, Vol. XXIII, 1875; Vol. XXIV, 1876.

Langley: Journal Physiology, III, 269, 1880.

Chittenden and Ely: Ibid., 327, 1880.

Roberts: 1880. (Roberts' Lumleian Lectures, 1881.)

Chittenden and Griswold: Amer. Chem. Journ., III, 305, 1881.

Kremel: Pharm. Post, 27–30, 1885.

Fairchild: Extractum Pancreatis, 1883.

Neumeister: Z. f. Biolog., XXIII, 381, 1887.

Chittenden and Painter: Stud. Lab. Phy. Chem., Yale Univ., II, 156, 1887.

König and Kisch: Z. f. Anal. Chem., XXVIII, 191, 1889.

Chittenden and Smith: J. Physiology, IX, 410, 1890.
Chittenden and Hartwell: Ibid., XII, 12, 1891.
Chittenden and Solley: Ibid., XII, 23, 1891.
Chittenden and Goodwin: Ibid., XII, 34, 1891.
Stutzer: Z. f. Anal. Chem., 31, 591, 1892.
Fairchild: Handbook of the Digestive Ferments, 1892.
Mett: Arch. des Scien. biolog., I, 142, 1894.
Siegfried: Z. f. Phy. Chem., 21, 360, 1894.
Chittenden and Mendel: J. Physiology, XVIII, 48, 1894.
Chittenden and Amerman: Ibid., XIV, 249, 1894,
Chittenden and Meara: Ibid., XV, 501, 1894.
Schoumow-Simanowski: Arch. Exp. Path. u. Pharm., 33, 336, 1894.
Wroblewski: Z. f. Phys. Chem., 21, 1895; Ber. de Chem. Gesell., 31, 1130, 1898.
Osborne and Campbell: J. Am. Chem. Soc., 17–22, 1895, 1900.
Pekelharing: Z. f. Phys. Chem., 22, 1896.
Kossel: Ibid., 22, 184, 25, 190; 26, 586; 28, 382, 1896, 1900.
Allen: Analyst, 285, 1897.
Pawlow: Arbeit. de Verdauungsdrusen, Bergmann, 1897.
Mann: Diss. Erlangen, 1897.
Mabery and Goldsmith: J. Am. Chem. Soc., XIX, 889, 1897.
Chittenden: Proc. Am. Phys. Soc., 1898, 3.
Chittenden and Mendel and McDermott: Amer. Jour. Physiol., 1898, 1, 255.
Bömer: Z. f. d. Unters. d. Nahrungsmittel, X, 160, 1898.
Wiley: Chem. News, 80, 88, 1899.
Mallett: Ibid., 80, 43, 117, 168, 1899.
Büchner: Arch. f. Klin. Med., 29, 537.
Fraser: J. of Anat. and Physiol,, 31, 469.
Friedenthal: Arch. f. Anat. u. Phys. Ph. Abth., 181, 1900.
Nencki and Sieber: Z. f. Phys. Chem. 27, 1901.
Oppenheimer: Die Fermente u. i. Wirkungen, 1900.
Green: The Soluble Ferments and Fermentation, 1901.

DOSE MEASURES AND MEASURED DOSES.

By M. I. Wilbert.

While dose measures have necessarily been in use as long as doses of medicines have been given, little attention has been paid to their

accuracy, or to the accuracy of the doses measured. It is true that occasionally we find an article calling attention to the variation in the shape and size of the different household utensils that are used as dose measures. But, so far as the writer's knowledge goes, no attempt has ever been made to inquire into the needs and necessities for obtaining more accuracy in the administration of potent medicines to the patient.

Some remarks that were made at a recent pharmaceutical meeting led the writer to try and investigate more fully the existing dose measures as to their efficiency and accuracy, and to further make some investigations as to the importance of the part played by personal equation in the measuring of doses.

To confine ourselves within reasonable limits we will not go into a discussion on metrology, nor will we take up the measures for larger quantities, but will restrict ourselves to a consideration of the ways and means for measuring out spoonful doses of active medicines.

The difference in the size of various tea and tablespoons has been recognized for a long time. More than twenty-five years ago Mr. Barnard S. Proctor brought the matter up for discussion before the Pharmaceutical Society of Great Britain. In the course of this discussion several substitutes were suggested, Mr. Proctor himself championing a cheap graduate marked in quantities of drams and ounces, ignoring any and all reference to the term spoon. Others suggested graduated glass measures similar to those used so extensively at the present time.

Among the other devices for overcoming what was thought to be a serious problem was the graduating of the medicine vial into tea and tablespoon doses, so that the patient in pouring out the medicine could tell whether or not the proper quantity was being taken. This same device has since come into extensive use in connection with nursing-bottles. Here it answers a double purpose: facilitating the proper mixture of milk, cream and water, and at the same time aiding the mother or nurse to keep an accurate account of the amount of food consumed by the child.

Still another device was the use of a half-ounce bottle as a measure for tablespoonful quantities; this could be graduated for teaspoonful doses by making a scratch at the proper position with a new or sharp-edged file.

Of late years, the number and variety of graduated medicine measures has not only increased, but improvements in the methods of manufacture have materially reduced their price.

Among the first graduated medicine measures was a porcelain spoon graduated in quantities of tea, dessert and tablespoons. The one on the table is of English manufacture, and a fair sample of the way these lines, or graduations, are usually found.

The next step in the evolution of a cheap medicine measure was a molded tumbler with lines on the outside of the glass. As illustrated by the samples on the table, these measures were usually very crude and rather ungainly. A decided improvement, so far as accuracy in indicating the contents of these measures is concerned, was made when the lines were put on the inside of the glass. To do this it was of course necessary to engrave corresponding depressions in the plunger used for molding the glass. The resulting lines are never very heavy, and often become entirely obscured when we attempt to measure dark or viscid liquids.

Hand-graduated tumblers are not to be forgotten; but these, especially in the earlier days, were rather expensive and not within the reach of any but the more opulent. At the present time, probably the most popular variety of a cheap tumbler is a combination having the lines engraved on the outside of the glass, while the quantities are indicated by molded numbers.

Before passing to a critical examination of these various measures, let us revert a few moments to the subject of spoons as measures of capacity. A spoonful is defined in English dictionaries as being as much as a spoon will hold. This rather loose definition is accepted as authoritative, in so far, at least, that every one using a spoon for measuring is allowed to put his or her own construction on what is meant by it. The French Codex, so far as the writer's knowledge goes, is the only authoritative work that defines exactly what is intended by the term spoonful. This book says, "A spoon is full when the liquid is on a level with, but does not show a curve above the upper edge or rim of the bowl."

Using this definition as our guide, we have made a number of examinations of spoons as found in use at the present time. The results thus obtained have been grouped in Table No. 1.

TABLE No. 1.—CAPACITY OF SPOONS, MEASURED ACCORDING TO DEFINITION OF FRENCH CODEX.

	Tea.	Dessert.	Table.
Tin	4·6		14·5
Plated, No. 1	5·0		14·3
2	5·0	10·0	14·8
3	4·8	9·0	15·0
4	4·8	9·0	14·6
Silver, 1	4·9		15·
2	5·2	9·4	14·8
3	4·9	9·6	15·4

In this connection we might say that the figures given are the average results of ten spoonsful of alcohol, it having been found that the necessary conditions were more readily obtained with this liquid than with water.

An examination of the table will reveal the fact, that when measured according to the definition of the French Codex, spoons do not vary to any considerable degree in their capacity. They do, however, differ considerably from the generally accepted equivalents as popularly used in this country at the present time.

The results, on the other hand, concur, in the main, with the equivalents given by the writer in an article on "A Metric Medicine Glass," published in the AM. JOUR. OF PHAR. for November, 1901.

In this connection, the writer would like to call attention to the desirability of recognizing, in an official way, the fact that the capacities of spoons in use at the present time conform very closely to metric quantities. Another point that the writer should be pleased to see taken up for discussion, is the question of definite values for the various approximate measures in the metric system. This would appear to be a timely problem and one that should be decided in some official method. At the present time, if a physician writes a prescription in the metric system, and abbreviates his directions to "5 c.c. T. I. D.," the pharmacist almost invariably transcribes this as "One and one-third teaspoonful three times a day," much to the confusion of the patient and also to the chagrin of the physician, who accuses the druggist of being behind the times, and not understanding the system of weights and measures according to which he is supposed to prepare his preparations.

It is popularly supposed that the ideal dose measure is to be found only in the graduated medicine glass; so much so, that authoritative works on pharmacy and therapeutics unhesitatingly recommend the use of these measures where any degree of accuracy is to be desired. It has even been asserted that these measures are invariably accurate and could be relied on to deliver the exact quantities intended by the prescriber.

Let us take up first the matter of accuracy. The price at which these measures are usually sold would evidently preclude any argument that a reasonable amount of care had been expended in their manufacture, or, that they had been individually tested as to their actual capacity at various points.

Admitting this, it need not surprise us if we find that, at times, these measures are not even approximately correct.

One peculiar feature of the problem is the fact that the more expensive medicine glasses are much more likely to be wrong than

TABLE No. 2.—CAPACITY OF MEDICINE GLASSES IN CUBIC CENTIMETRES.

Glass No.	Teaspoon.	Dessertspoon.	Tablespoon.	2 Tablespoons.
Normal	3·7	7·4	14·8	29·6
1	3·0	5·2	12·2	27·5
2	6·4	8 8	16·4	33·5
3	4·8	8·4	14·8	31·0
4	3·5	7·0	14·2	29·5
5	3·6	7·0	14·6	30·0
6	3·2	7·2	14·8	32·
7	5·0	9·0	16·0	31·6
8	4·1	7·1	15·2	34·0
9	4·9	8·2	14·8	31·0
10	3·5	7·2	14·4	31·0
11	4·2	9·2	17·2	33·0
12	3·6	6·8	13·2	30·5
13	4·2	7·8	15·2	34·5
14	3·8	7·6	15·2	31·0
15	4·3	8·2	16·0	
Metric normal . . .	5·0	10·0	15·0	30·
16	4·1	8·2	16·0	33·6
17	4·9	10·3	15·2	30·
18	4 5	9·6	15·0	

are the cheaper variety that may usually be purchased for a mere trifle.

We have measured a number of these glasses and tabulated the results in Table No. 2. In explanation, the writer would like to say that with but few exceptions all of these glasses are samples obtained from manufacturers or dealers, and that the figures are, as in the case of the spoons, average results of ten or more measurements for each quantity, made as nearly as possible under the same physical conditions.

It will be noted that there is a marked difference in the quantities measured from the various measures, and that some of these glasses vary at different points. An attempt has been made to demonstrate the reasons for this, and at the same time to illustrate the difficulty most persons would have in attempting to measure small quantities from some of these graduated measures.

Table No. 3 gives the inner diameter of the various glasses at the

TABLE No. 3.—GIVING DIAMETER OF MEDICINE GLASSES IN M.M.

Glass No.	Teaspoon.	Dessertspoon.	Tablespoon.	DISTANCE IN M.M. FROM	
				Bot'm to Table.	Tea to Table.
1	28'	30'	35'	13'5	11'
2	33'	34'	36'	18'5	11'
3	35'	35'5	37'5	15'	10'
4	34'	37'	40'	13'5	10'5
5	40'	40'5	42'	13'	9'
6	33'	34'	37'	14'	11'5
7	39'	40'	42'	14'	8'
8	35'	36'9	39'	16'	10'
9	31'	32'	34'	18'5	12'
10	27'	29'	31'5	23'	16'5
11	27'5	30'	35'	29'	17'
12	27'	30'	34'	21'	15'
13	30'	32'	35'	22'	15'
14	29'5	32'	34'	21'	16'
15	26'	27'5	31'	26'	18'
16	29'	31'5	34'5	22'	16'
17	30'	32'	34'	21'5	14'
18	26'	28'	30'		

tea, dessert, and tablespoon mark, and also, as nearly as this is possible, gives the distance in millimetres, from the bottom of the glass to the tablespoon mark, and then the distance between the tea and tablespoon mark.

A description of the methods used for graduating these measures would not be out of place, and will serve to explain some of the variations in capacity.

For a cheap measure the lines blown or molded on the outside of the tumbler are the ones most readily available. These lines may be made quite heavy and distinct, but it will, necessarily, be very difficult, if not well-nigh impossible, to get two glasses exactly alike, on account of the variation in the amount of glass entering the mold and the consequent difference in their inner capacity. This type of glass is illustrated by numbers 10 and 11.

The next has the marks placed on the inside of the glass by a graduated plunger. If the plunger is accurately graduated this method will give quite uniform results for the same lot of glasses. Numbers 12, 13 and 16 are glasses of this variety, and illustrate the possible variation due to different plungers. These glasses also illustrate the fact mentioned a few moments ago, that these lines are sometimes very faint and easily obscured by a dark or viscid liquid. This is due to the fact that the plunger cannot be deeply engraved, as this would interfere with its consequent withdrawal from the finished glass.

Engraved glasses appear to be graduated according to one of the following methods:

Where a pressed glass is used for graduation, it is customary for some manufacturers to accurately measure and graduate one glass as a sample; from this they graduate a wood block, and this block is subsequently used as a pattern to graduate the remaining glasses made from this particular mold. Glasses graduated in this way seldom vary more than 10 per cent. The cause of variation is a slight difference in the internal diameter of the glass, or a slight elevation or depression of the bottom of the tumbler that prevents the gauge block from going to its proper position. Numbers 14, 15 and 17 are made according to this method, and are fair specimens of the results.

The next method, and the one that is used almost exclusively on the higher priced glasses, is to measure into a glass a certain quan-

tity of water, usually one tablespoonful. The glass is carefully marked at this point, then another tablespoonful of water is run in, and this point is also marked. This marked glass then goes to the engraver, who cuts the graduations in at the points that are marked, and then, either promiscuously or according to some fixed rule, the intervening space is marked off and graduated to represent the fractional parts of a tablespoonful. The glasses from 4 to 9 are examples of this style of measure and fairly represent the shortcomings of this method of graduating glasses. The third method of graduating plain glasses appears to be by the rule of thumb, and consists simply of putting on the outside of the glass the requisite markings according to some fixed scale or pattern. This style of graduation is always readily recognized, the lines are always in the same relative positions, regardless of any variation or difference in the shape, size, or thickness of the glass itself. Numbers 1 and 2 are samples of this style of graduations.

The variations that exist in some of the other medicine measures are shown in Table No. 4. Among these we have the porcelain

TABLE NO. 4.—CAPACITY OF OTHER MEDICINE MEASURES.

Porcelain graduated spoon	3.5	7.2	14.2
Glass graduated spoon	3.0	6.5	14.8
Glass medicine spoons	4.0	6.0	16.0

medicine spoon, referred to before, as being a type of an early attempt to replace spoons by some more accurate means of measuring.

Recently a pressed glass graduated spoon has been put on the market. As a measure this has no advantages over the porcelain spoon just referred to, and it would appear to be of but slight use as a carrier or vehicle with which to administer doses.

Glass medicine spoons have been used to some extent, but these are to be classed among the most variable of all medicine measures.

A review of this portion of our investigations would appear to bring out the fact that these medicine measures vary as much as 70 per cent. at the teaspoonful mark; this graduation should really be the most accurate, as medicines that are given in teaspoonful quantities are necessarily more active than those given in larger amounts, so that a variation at the lower mark would appear to be of relatively more importance than the same variation at the graduations for larger quantities.

This actual variation in shape, size and capacity of medicine-glasses is but one side of the problem; another, and probably a much more important part, is played by the personal equation, or ability, of the person that is actually doing the measuring. This factor is usually lost sight of in discussions of this kind, but is really of considerable moment, especially when we consider that doses are necessarily measured by all classes and kinds of people that may, or may not, have had training in this particular direction.

To get some approximate ideas as to the real importance of this personal equation factor, we have made several hundred investigations or trials on, or with, upwards of a hundred people. Representative medicine measures were taken, and the various persons were requested to measure out ten doses, just as though they were to be given to a patient. For the liquid, a diluted alcohol, slightly colored with caramel, was used. An alcoholic mixture was chosen so as to reduce as much as possible the error resulting from portions of the liquid remaining adherent to the sides of the glass. The doses were measured into a beaker or glass tumbler so as to avoid any suggestion that might be offered by the lines and figures on the sides of a graduate. The total quantity was later measured, and this total, divided by ten, gave us the average for the individual doses. By measuring twenty doses alternately, in two separate tumblers, it was found that the averages were remarkably even, so that for all

TABLE NO. 5.—SHOWING HIGHEST, LOWEST AND AVERAGE QUANTITIES MEASURED FROM THE SAME MEASURE BY VARIOUS PERSONS.

TEASPOONS.				TABLESPOONS.		
High.	Low.	Average.	Glass No.	High.	Low.	Average.
3·6	1·5	2·5	4	15·2	11 6	14·4
3·4	2·1	3·0	5	14·5	10·8	12·8
3·5	1·8	2·6	6	13·8	11·5	12·6
4·9	3·0	3·9	13	16·6	12·0	14·2
5·2	3·1	3·8	14	16·6	12·0	15·0
4·4	3·5	4·1	15	16·2	14·0	14·8
6·0	3·2	4·4	17	16·2	12·3	14·9
7·0	3·0	5·0	Spoon.	18·0	8·9	14 0
4·2	2·0	3·2	Med. spoon.	16·4	12·2	14·2
5·1	4·5	4·8	Special.	15·2	14·6	14·9

practical purposes there was no decided element of error to be taken into consideration.

Table No. 5 shows some of the results, and illustrates the highest and lowest dose averages obtained from several of the medicine measures used. When we compare the results given here with the diameter of the glasses as given in Table No. 3, we learn that the cheapest available medicine-glass may be considered the most accurate for all around use. This is due to the fact that the manufacturer, in the first place, graduates these measures nearly correct; and, secondly, that in the subsequent use for measuring, a slight variation of the resulting meniscus above or below the line is of comparatively little moment. With wide glasses, on the other hand, a slight variation of the engraved line, by the maker, or a corresponding variation of the meniscus of the liquid being measured, makes a decided difference in the amount of liquid actually measured.

Here again we may note that the variations at the teaspoonful quantities are comparatively much greater than at the tablespoon.

Altogether these tables would appear to contain much food for thought, and in a general way indicate the lines on which a more accurate and reliable medicine measure might be made.

Another series of experiments, made with a view of obtaining some data as to the value of experience in measuring doses, are shown in Table No. 6. These experiments were again made with tea and tablespoonful doses, and the tables give the highest, lowest and average quantities measured by respectively ten patients, ten nurses, and ten physicians.

As was to be expected, the greatest amount of variation occurred, of course, in the use of the spoon; this is accounted for by the fact that there is a decided difference of opinion as to what constitutes a spoonful, some people considering a spoon full when it is filled to a point where it would become difficult to carry it about without spilling some of its contents. Others, on the other hand, appear to contend that a spoon is not full "Until it doth run over;" it is easily seen, therefore, how in the one case we may have as the result more than donble what we had in the other.

Pretty much the same thing occurs, however, with a medicine-glass; very few people, unless previously instructed, have any idea how to measure with a graduated measure, the great majority reading from the upper edge of the resulting meniscus, so that under

TABLE NO. 6.—SHOWING HIGHEST, LOWEST AND AVERAGE QUANTITIES MEASURED FROM THE SAME MEASURE BY, RESPECTIVELY, TEN PATIENTS, TEN NURSES, AND TEN PHYSICIANS.

TEASPOONS.				TABLESPOONS.		
High.	Low.	Average.	Patients.	High.	Low.	Average.
7·0	3·0	5·2	Spoon.	18·0	8·9	13·5
5·2	3·2	3 8	Glass No. 14.	16·2	12·0	14·2
6·0	3·4	4·4	Glass No. 17.	15·6	12·3	14·4
High.	Low.	Average.	Nurses.	High.	Low.	Average.
6·7	3·6	4 8	Spoon.	16·2	12·6	13·9
4·4	3·5	3·8	Glass No. 14.	16·4	13·0	14·9
5·2	3·2	4·6	Glass No. 17.	15·0	13·2	14·5
High.	Low.	Average.	Physicians.	High.	Low.	Average.
5·8	3·8	4·9	Spoon.	15·6	12·0	14·4
4·8	3·1	3·9	Glass No. 14.	16·6	14·8	15·7
6·0	3·6	4·8	Glass No. 17.	16·2	13·8	14·9

certain conditions a patient may, at one time, get more than double the dose of an active medicine than he has been in the habit of having. Altogether, the possible results from variations of this kind are not in keeping with modern ideas of scientific medicine. Several other interesting features were developed in the course of these investigations: one of them is the fact that the majority of people measure out larger doses from a small bottle than they do from one three or four times the size. Using the same liquid and the same measure, the variation in the size of the doses measured reached as much as 20 per cent. The reason for this particular difference was not developed, but it was probably due to some suggestive influences.

Another interesting variation was noted in connection with spoons. It appears that individuals using the same spoon almost invariably measure out more when using a colorless fluid than when using one that has a decided color. In some cases this difference has reached as much as 70 per cent. This variation was found to be more marked in artificial light. This latter incident probably gives the clue for a solution of this particular problem. The direct cause for

the variation probably being the fact that a colorless fluid is not so readily seen against a bright shining spoon as is one that has considerable color.

Suggestion is a factor that plays an important part in experiments of this kind, and at times, at least, is very difficult to guard against. Just one case to show how easy it is to influence even most intelligent people:

A particularly careful physician was asked to measure out doses with the various measures, and after obtaining several averages it was suggested that he try measuring teaspoonsful of a colorless fluid just to notice the difference in the size of the doses. His averages in this case were slightly below his corresponding averages for the colored liquid. When told that his results in this particular test varied considerably from those obtained by others, he volunteered to try again, and despite the fact that he asserted the quantities to be no larger than before, his averages in this case were nearly one-fourth greater.

There is one other feature of the personal-equation factor that might be mentioned in this connection; this is the variation that occurs in measuring doses of medicines that contain opiates. It is not an uncommon occurrence to have customers who have this class of prescriptions refilled at gradually shortening intervals. This would indicate one of two things: either the patient was taking more doses than the physician prescribed, or his dose-measures were gradually becoming larger; at any rate, it is one of the many possible abuses that should be guarded against by the pharmacist.

Having enumerated a few of the possible sources of error in measuring doses, the question naturally arises, Is there any possible remedy to correct these various discrepancies?

The solution of the problem that suggested itself to the writer's mind is a rather tall and narrow measuring-glass, on which the teaspoonful quantity is correctly indicated. With such a medicine measure there would be but slight chance of any grave or glaring error, either in its manufacture or its subsequent use.

The subject of drops and droppers was taken up later, with a view of determining what, if any, difference existed between the drops from various shapes and sizes of so-called medicine-droppers. This simple device is now in such general use in this country, and the number of very active drugs that are measured out in drop

doses is increasing to such an extent, that an inquiry into the possible variation in the size of the drops was thought to be of considerable and timely interest, especially in view of the fact that the Pharmacopœial Revision Committee has before it a proposition to adopt an official or standard dropper.

The literature on the subject of drops is quite extensive. The files of the AMERICAN JOURNAL OF PHARMACY alone contain numerous and exhaustive papers on this subject, and many, if not all, text-books and commentaries have considerable amount of space devoted to a more or less exhaustive review of the subject, and also the more or less reliable tables of the number of drops of various liquids that are necessary to measure a fluid dram. Many, if not all of the investigations that are usually quoted, were carried out by dropping either from the lip of a bottle, the edge of a cork, or the lip of a minim graduate. As far as the writer's knowledge goes, no extensive investigations have been made into the subject of drops from the much-used medicine-dropper.

In dropping liquids from a pipette it is essential that the latter be held point down, if correlating results are to be obtained. In actual practice this necessary precaution does not appear to be recognized or appreciated. In some experiments that were made to determine what, if any, effect personal equation would have on the number of drops necessary to weigh one gramme, it was noted that comparatively few people held the dropper point down, but that the majority held the pipette at such an angle that the drop was formed from the side rather than the point of the dropper. That a difference in the way a pipette is held has a most decided effect on the size of the resulting drop is well illustrated in Table No. 7.

Few people would admit that there could be such a variation in the size of drops from the same dropper, but a series of experiments, that any one can conduct for himself, will be the best way of convincing them of this fact. One question naturally arises: What dependence can be placed in the extensive drop-tables usually published in works of reference? Here, again, the answer must be with the individual, and the only suggestion that the writer wishes to offer is, that it may at times be well for the individual to try and duplicate some of the quantities stated according to his own methods or ideas.

TABLE No. 7.—SHOWING NUMBER OF DROPS REQUIRED TO WEIGH 1 GRAMME.

			DIST'D WATER.		DIL'D ALCOHOL.		ALCOHOL.	
	Diameter.	Normal.	High.	Low.	High.	Low.	High.	Low.
Straight	3 m.m.	20	26	13	50	20	68	45
Ground	3 m.m.	20	25	18	54	42	73	52
Short taper	3 m.m.	20	20	10	44	26	54	33
Bent	2 m.m.	28	32	10	70	30	90	35
Exact	3 m.m.	20	22	10	48	26	65	36
French	7 m m.	10	14	10	40	24	47	29
Large bulb	18 m.m.	8	9	8	22	20	28	26
Decigramme	9 m.m.	10	10·5	9·5	28	25	36	33
Dropping bottle		10	12	10	33	29	36	32

One thought that was suggested by the results obtained was, that a drop of water, weighing the one-tenth part of a gramme, was a relatively more constant quantity, and one that could be more easily duplicated, than the proposed standard drop weighing the one-twentieth part of a gramme. This proposed standard drop is rather difficult to obtain without considerable variation or error. One improvement in the pipette, as proposed by Dr. Seaman to the Pharmacopœial Revision Committee, suggested itself. This is, to grind the lower edge or mouth of the pipette; this appears to retard the crawling up of the liquid and the consequent increase in the dropping surface. But even with this modification, we still have a possible variation of more than 30 per cent.

If we modify the "French pipette" in the same way, we can reduce the variation to less than 20 per cent.; and in addition to this we would practically establish the proposition that a drop of distilled water is a metric quantity, being equal in weight to one decigramme, or in bulk to the one-tenth part of a cubic centimetre.

It is possible, however, to bring the drop of distilled water still nearer to a fixed metric standard. If we had a perfectly round sphere, of from 7 to 9 m.m. in diameter, arranged so as to allow drops of water to form and drop from it, we would find that these drops were so regular in size and weight that they might be used as a standard of weight and bulk. To all intents and purposes this would at least equal in accuracy the plump grain of wheat that is the standard of weight for the various systems at the present time.

As such a sphere is not readily adapted to be used as a dropping pipette, the writer has devised a simple spherical outlet to an ordinary pipette, and with a dropper constructed on this principle it is possible to drop, either from the sides, bottom or edge of the tube, drops that will weigh, within a minute fraction, one decigramme. So constant are these drops as to weight and size that 10 will weigh one gramme, and 100 will weigh 10 grammes or measure 10 c.c., with a possible variation of less than 5 per cent.

From a series of experiments that have been made, it may be said that this ratio is fairly constant, for all aqueous liquids or solutions, as to weight but not measure. The relative number of drops of alcohol may be said to be three to one of water, and of dilute alcohol about two and a half to one of water. This latter proportion is perhaps a little high, and for all practical purposes the following ratio may be taken as representing a fair average: Water, 1; diluted alcohol, 2; alcohol, 3.

In conclusion, the writer would suggest that a perfectly made decigramme pipette may simplify the relative size and weights of drops, and would also offer an additional argument for the introduction and use of the metric system of weights and measures.

A METHOD OF DETERMINING THE SOLUBILITY OF ALKALOIDS.

By Robert A. Hatcher, M.D.

In attempting to dissolve cinchonine in water much difficulty was experienced, owing to the fact that the powder floated upon the surface of the liquid or clung to the sides of the vessel.

The alkaloid was then dissolved in alcohol and added to water, the alcohol being expelled by heat; but this method proved no more satisfactory than the first mentioned.

The cinchonine was next rubbed with water until a smooth mixture was made; to this was added from a burette the requisite amount of $\frac{N}{10}$ H_2SO_4 to convert it into the sulphate, and solution easily effected. Portions of this were diluted in various proportions, and to each a slight excess (about 2 c.c.) of $\frac{N}{10}$ NaOH added; from the relative amounts precipitated in the various dilutions an

estimate of the amount remaining in solution was gained, and a new series of dilutions made and precipitated as in the foregoing. That solution which gives a barely perceptible precipitate, using a control solution for comparison, is taken as the solubility, or this dilution and the lowest giving no perceptible precipitate are taken and the solubility is reckoned as the mean of the two. Applying this method to morphine, it gave results agreeing with the solubility given by the Pharmacopœia.

I therefore suggest the following method of finding the solubility of those alkaloids which do not readily dissolve in water:

Take 0·1 gramme of the substance, rub with water to a smooth paste and then with water until a smooth mixture of about 9 c.c. is obtained, to this add enough N H_2SO_4 from a burette to convert the alkaloid into the sulphate, and then enough water to make 10 c.c. of solution; of this take portions of 1 c.c. each and dilute in several proportions; to each add a slight excess of N NaOH, and from the relative amounts of precipitate estimate the solubility; again, take several portions of 1 c.c. each and dilute to approximately the point of saturation, in one case using higher and in another lower dilutions; again, precipitate with slight excess of NaOH, and more accurately estimate the solubility. From a third series, using the second estimate as a basis, the solubility may be learned by taking the mean of the highest giving a precipitate and the lowest giving none that is perceptible.

I would also suggest the application of this method for testing those alkaloids, the solubility of which is known. Thus, morphine is soluble in 4350 parts of water; and if 0·1 gramme morphine be rubbed with water and then with enough N H_2SO_4 to convert it into the sulphate and diluted to 10 c.c., and two portions of 1 c.c. each of this be further diluted to 43 c.c. and 44 c.c., including the requisite amount of N NaOH to give a very slight alkalinity, a slight turbidity or precipitate should be found in the first and none in the second, from which is taken the mean, or 1 part in 4350, as the solubility of morphine. Of course, in the case of expensive alkaloids, 0·01 gramme may be used instead of 0·1 gramme, but more accurate results will be had by using the larger quantity.

THE SOLUBILITY OF CINCHONINE.

By Robert A. Hatcher, M.D.

Being requested to examine a specimen of cinchonine from a reputable manufacturer (Schuchardt), which was sold as pure, the pharmacopœial tests were applied, including those for the detection of other cinchona alkaloids, melting point, solubility in alcohol, ether and water. It conformed to every requirement save that of solubility in water.

The Pharmacopœia states that cinchonine is soluble in 3,760 parts of water. Roscoe and Schorlemmer quote Hesse, giving the solubility as 1 to 3,670 at 20°, 1 to 2,500 at the boiling point. I regret that I have not access to the original paper, as there is evidently a typographical error in one of these, transposing the 6 and 7.

The difficulty experienced in effecting solution led to the device which is the subject of the preceding article. Prolonged boiling in 15,000 parts of water proved ineffectual, none seeming to have dissolved. Having added an alcoholic solution to water, the amounts precipitated from dilutions of 1–10,000 and 1–20,000, while none precipitated from the 1–25,000, furnished an approximate idea of the solubility.

The method just described was used, 0·1 gramme being dissolved in 90 c.c. of water with the aid of $\frac{N}{10}$ H_2SO_4, and enough water added to make the volume up to 100 c.c. Several portions of 10 c.c. each of this solution were diluted to 150 c.c., 200 c.c. and 250 c.c., respectively, making dilutions of 1–15,000, 1–20,000 and 1–25,000. To each of these was added a slight excess of $\frac{N}{10}$ NaOH; the weakest solution showed no precipitate, the next showed some, and the strongest considerable. The solubility evidently lay between 1–20,000 and 1–25,000. The process was now repeated, using 10 c.c. and diluting to 1–20,000, 1–22,000 and 1–24,000. Upon adding a slight excess of $\frac{N}{10}$ NaOH to each, and cooling to 21° C. for about 12 hours, a slight precipitate was observable in the dilution of 1–22,000, but none in that of 1–24,000. The mean was taken as the approximate solubility of cinchonine—1–23,000—and this is as near the exact figure as can be attained by ordinary procedures,

the nature of cinchonine and the presence of certain insoluble particles which pass through the filter, serving to obscure the more exact results.

Upon adding the exact equivalent of $\frac{N}{10}$ NaOH for the H_2SO_4 employed, no precipitation occurred even upon cooling stronger solutions to 20° for 24 hours, hence the slight excess of alkali was employed.

A TRUE BENEFACTOR.

By William B. Thompson.

The announcement of the death of Prof. Emil Scheffer, of Louisville, Ky., at the honorable and unusual age of 90 years—almost patriarchal in duration—recalls to the recollection some interesting facts . It is now thirty years since Professor Scheffer generously gave to scientific knowledge the result of his studies, and the exact determination of the nature and physical character of that chief factor of peptic-ferment, pepsin. Previous to Professor Scheffer's successful and valuable labor no distinctive isolation of pepsin, as a substance, had been made. French scientists had recognized the fact that there existed a normal agent in the gastric and digestive fluid of the stomach, and had even traced its origin to a secretion from the mucous folds of that organ and of the intestinal tract. There was a theory that it was only in the living organism that this peculiar and potent agent exercised its action, and that with the cessation of vitality it at once became inert. Thus it was that the separation, or elimination, if attempted at all, was merely a mechanical process, accomplished by scraping the separable mucus from the walls of the stomach of mammals. Therefore, the pepsins of the then almost wholly foreign commerce consisted of mucus artificially and imperfectly dried with, possibly, some semi-converted food, as peptone, and an absorbent medium, such as starch, with the addition of a proportion of lactic acid to complete the imaginary character. From this it will readily be observed that there was nothing whatever of definite existence or proportion; and whilst such substance found its way into medical adoption, and useful results were thought to be traceable to it, it could not be considered other than a crude and unsatisfactory product. The older pharma-

cists will well remember the intractable character of the American imitations of that former day and the vexatious attempts to bring it into pulverized accord with accompanying components of prescriptions. With the successful completion of Professor Scheffer's labors and determining experiments, he gave to the world, in pamphlet form, a clear and comprehensive résumé of all the various steps of process of preparation, a minute description of the properties of pepsin, its behavior to other substances, its assimilation, and its antagonistic associations. For this most unselfish, generous, and liberal spirit the victims of pain and suffering everywhere, the votaries of science, the medical profession, and the exponents of pharmaceutical research have incurred a debt of unrequitable gratitude, and owe that fullest meed of honor and praise that is ever the tribute of sincere appreciation. By this act Professor Scheffer bestowed upon commercial enterprise, without reward, an article of manufacture, which not only amply enriched those who appropriated it, but which added wealth to the material productions of our country. Alas! there are but few to be found now of that nobler mold of mind and spirit which actuated this man. The demon of individual grasp and greed, the clutch for self-gain, now suppress all higher instinct, and make of the discoverable benefactions to mankind a secret of trade, to be accorded to general use only when some selfish desire for pecuniary benefit is amply recompensed.

Professor Scheffer labored in the ranks of pharmacy, with which pursuit he was immediately identified. Let the honor due his labors be felt and appreciated by his confrères, and let his name be enrolled on the scroll of benefactors of mankind.

SOME RECENT DRUG ADULTERATIONS.

By Lyman F. Kebler.

According to the First Annual Report of the New York State Board of Pharmacy to the Governor, 3,390 medicinal remedies were examined, and of this number 2,637 were adulterated, or not up to the required standard. These drugs were purchased from all sections of New York State—Eastern, Middle and Western—and that over 77 per cent of such a collection should be of inferior quality is hardly creditable. The writer has kept watch of the wholesale trade in Philadelphia for the past six months, and finds that his

former statement relative to the percentage (less than 5 per cent.) of adulterations met with well covers this point.

The following interesting adulterations have been met with by the writer and other workers in various sections of the world:

ARTIFICIAL CINNAMON BARK.

Guava (Jungle Bark) can be placed on the Columbo market at a very reasonable price. This bark resembles cinnamon bark very closely, and, consequently, certain unprincipled individuals have taken this bark, scented it with oil of cinnamon, or the by-products in the distillation of the cinnamon oils, and offered it as cinnamon bark. A superficial examination of this bark would not reveal its identity.—*Pharm. Centralblatt*, 42, 526.

CROTON OIL IN TINCTURE OF IODINE.

It has been reported that the above oil has been found in tincture of iodine. (Tincture of iodine and croton oil resemble each other in that they are irritants to the skin, but here their similarity ends. No one would ever think of applying croton oil where iodine was indicated. Whether the above adulteration is an ingenious one from the druggist's point of view is questionable. The object, of course, was to make the tincture more efficient by using a small quantity of croton oil. When it is remembered that croton oil will take up, at least, 100 per cent. of iodine, and thus tend to make the tincture of a lighter color, and at the same time it is questionable whether the hypothetical "Crotonoleic Acid" will retain its normal irritating properties when combined with iodine, such an admixture would, on general principles, be considered very injurious. L. F. K.) —*Brit. and Colonial Drug.*, 40, 176.

A NEW ADULTERATION OF BERGAMOT.

Dr. Salvatore Gulli (*Chemist and Druggist*, 59, 699) notes that the commercial adulteration of oil of bergamot, by means of either the crude or other inferior bergamot distillates, or by isomeric peel essences, has almost ceased, because the normal physical properties are usually abnormally distributed by such addition. New falsifications are, however, making their appearance. One of the ingredients chiefly distributed is the per cent. of linalyl acetate, which it is the desire of the manipulator to be

as high as possible, because this is frequently the basis of a purchase. With this object in view, he diligently seeks to add some material which will bring up the ester content of an inferior oil. This he has found in bi-hydrochloride of terebinthin, or other products resulting by the action of hydrochloric acid gas on turpentine. These chloro-derivatives are decomposed when submitted to the usual alcoholic potash saponification process, and consequently the apparent quantity of ester is increased.

From 5 to 10 per cent. of these chloro compounds when added to oil of bergamot are sufficient to raise the indicated per cent. of linalyl acetate without materially disturbing the normal properties of the oil, as is clearly shown by the examination of a number of commercial samples of oil of bergamot which contained the above chloronated turpentine compound.

No.	Specific Gravity at 15° C.	Opt. Rot. at 20° C. in a 2 cm. tube.	Per Cent. of Ester.
1	0·882	+10·5°	36·05
2	0·8817	+ 8°	36·75
3	0·8810	+ 6°	36·40

It will seen from the above figures that these oils are normal in every respect; nevertheless, they were all adulterated with from 5 to 10 per cent. of this artificial chlorine product. The presence of this impurity is not very easy to detect, and the above writer recommends the following process: Boil several grammes of the suspected oil with alcoholic potash, evaporate gradually, and then calcine so as to get rid of the organic matter; treat the resulting residue with distilled water, filter and test the filtrate for chlorides in the usual way.

HONEY ADULTERATED WITH SUCROSE.

Recently a sample of honey was examined by the writer with the following results: Specific gravity at 15° C., 1·354, acid reaction; pollen grains, none; moisture, 24½ per cent.; ash, 0·21 per cent.; optical rotation, direct, + 9½ divisions sugar scale, at 25° C.; optical rotation after inversion, — 11·6 divisions on the sugar scale, at 25° C.; reducing sugar direct, 54 per cent.; reducing sugar after inversion, 63·50 per cent.

The above figures all indicate the presence of added cane sugar. The dextro-rotatory power of the honey was apparently ample to decide that it contained cane sugar, because, as yet, we have no

genuine honey of this country reported as being dextro-rotatory, and until such an authentic observation is made, which is possible, a dextro-rotatory honey must be looked upon with suspicion.

THE ADULTERATION OF ERGOT OF RYE.

The Paint, Oil and Drug Reporter contains a letter which informs us that ordinary rye ergot is being at present largely adulterated with ergot of wheat and barley to the extent of from 30 to 40 per cent. If this condition of affairs exists, it certainly is very unfortunate, because very few manufacturers in this country are in position to detect such adulteration. While it is generally known that rye ergot contains more or less of the wheat ergot, it is generally believed by those in a position to know that this practice does not exist to the extent of 30 to 40 per cent. In the first place, ergot of wheat is comparatively a scarce article. It might also be mentioned in this connection that various authorities who have examined these ergots find that the wheat ergot is probably as efficient as rye ergot. In fact, the wheat ergot seems to retain its active properties longer than the rye ergot.

VANILLA BEAN, ADULTERATED.

Henri Lecomte (*Bull. des. Sc. Pharmacolog.*, 1901) notes that the presence or absence of a crystalline coating on the vanilla bean is no indication of its quality. According to this author, the Mexican vanilla beans, which are classed among the best, are always without these crystals. He further states that the crystalline appearance is frequently an artificial covering produced by the addition of benzoic acid. This adulteration can easily be detected by determining the melting point of the crystalline coat. The character of the crystals can be detected by dissolving a trace of phloroglucin in alcohol on a watch-glass, adding an equal volume of hydrochloric acid; then introducing, by means of a slender glass rod, one or more of the minute crystals from the vanilla pod into the mixture, and a beautiful red color will be produced, if it is vanillin, whereas benzoic acid crystals will leave the mixture colorless.

IMITATION PEPPER.

Artificial pepper has been found in the Switzerland market. These artificial pepper corns are slightly smaller than the genuine berries,

and somewhat heavier than water. In water they quickly disintegrate, dissolving in part; the remaining portion subsides in the form of powder. One variety consisted, for the most part, of starch mixed with soluble binding material. Another variety appeared to come from an olive-oil industry, where the residue, which appears in commerce as "sansa," was utilized. The surface of the black berries was covered by means of sand-colored black. Both varieties manifest a burning taste, which was due to the admixture of a little paprika.—*Schweiz. Wochenschr. f. Chem. u. Pharm.*, 39, 1901.

BEESWAX.

As usual, beeswax has contributed its quota of samples, more or less adulterated, as the following results will show:

Kind.	Melting Point.	Specific Gravity at 15° C.	Acid No.	Ether No.
White . . .	64° C.	0·926	6·2	66·6
Yellow . .	64° C.	0·938	12·9	60 9
Yellow . .	55° C.	0·9138	10·9	22·6

The above data clearly indicate that the samples examined were liberally adulterated with ceresin, although this is not the only adulterant added, as is clearly seen by the ratio that exists between the acid and the ether numbers. Tallow or a similar substance, which will bring up the ether number and not the acid number, is manifestly indicated by some of the above figures.

OIL OF WORMWOOD.

Quite a considerable quantity of this oil has been found adulterated, the usual diluent being turpentine. The following results were obtained while making an examination of a number of samples submitted:

No.	Specific Gravity at 15° C.	Solution in 2 Vols. 80 Per Cent. Alcohol.	Solution of 1st 10 Per Cent. of Distillate in 2 Vols. of 80 Per Cent. Alcohol.
1	0·9128	insoluble.	insoluble.
2	0·9104	"	"
3	0·9362	soluble.	soluble.
4	0·9071	insoluble.	insoluble.
5	0·9262	soluble.	soluble in 2–3 vol.
6	0·9299	"	———
7	0·9364	"	soluble.
8	0·9112	insoluble.	insoluble.

The normal properties of oil of wormwood are: a somewhat viscid liquid of a dark-green color, odor unpleasant and taste somewhat

bitter and persistent. Specific gravity, 0·925–0·955. On account of its dark color it is difficult to determine the optical rotation generally. The oil itself is soluble to a clear solution in from two to four volumes of 80 per cent. alcohol. On submitting the oil to fractional distillation the first 10 per cent. of the distillate is soluble in two volumes of 80 per cent. alcohol. From the above data it can readily be seen that numbers 1, 2, 4 and 8 are deficient in a number of points, and careful investigation showed that these oils were liberally adulterated with oil of turpentine. The turpentine odor was even perceptible to the nose in several samples.

Laboratory of Smith, Kline & French Co.
Philadelphia.

RECENT LITERATURE RELATING TO PHARMACY.

ESTIMATION OF PHENOLS, WITH SPECIAL REFERENCE TO OIL OF CLOVES.

Verley and Bolsing publish a paper (*Berichte*, 1901, 3354) on the determination of alcohols and phenols, especially in essential oils, by a method they have elaborated. In a second paper they deal with the special applicability of the process to oil of cloves for the determination of the eugenol. The principle of the process is the esterification of the alcohol of phenol with acetic anhydride, with the addition of pyridine, which serves to retain the acetic acid formed during the esterification, thus preventing the reverse process of hydrolysis going on. The actual details of the process are as follows:—

One hundred and twenty grammes of acetic anhydride and 880 grammes of pyridine are mixed, care being taken that no traces of water are present. No reaction takes place, but on the addition of water the anhydride is decomposed with the formation of pyridine acetate, which is easily saponified by alkali. The acetic value can thus be obtained for the mixtures. From 1 to 2 grammes of the substance to be examined is introduced into a flask holding about 200 c.c., and 25 c.c. of the mixture of acetic anhydride and pyridine is added. It is then heated for fifteen minutes on a water-bath without a condenser, which appears to be unnecessary, and after cooling 25 c.c. of water is added, and the free acetic acid titrated with potash, using phenolphtalein as indicator.

A number of results are given, some being of almost theoretical

accuracy, and some are very much lower than they should be. Whilst correct results may follow in some cases, careful investigation is needed before the process can be said to be as accurate as the well-known acetylation method. This is well emphasized in the case of sandal oil and santalol. It is established that no pure sandal oil yields less than about 90 per cent. of santalol, and that pure santalol yields results agreeing with over 100 per cent., rather than under; but the new process gives only 81 per cent. for the oil, and 95 per cent. for the pure alcohol.

The second of the papers deals with Umney's and Thoms's processes for the determination of eugenol in oil of cloves. It is pointed out (as is well known) that the use of 10-per-cent. alkali causes some of the non-phenolic constituents of the oil to be absorbed, but that better results are obtained by the use of 3 to 4 per cent. alkali. Indeed, oils prepared by mixing known quantities of eugenol and terpenes gave results within 1 to 2 per cent., and very reliable results may usually be obtained by the absorption-process with dilute alkali. Three samples were prepared from pure eugenol and pure sesquiterpenes of 85 per cent., 90 per cent., and 95 per cent. strength. The three results in each case are as follows:

	Per cent.	Per cent.	Per cent.
Actual eugenol value	85·0	90·0	95·0
Acetic pyridine method	84·4	89·5	95·9
Absorption process (dilute)	85·3	90·0	95·0
Thoms's process	81·5	87·2	91·4

Two samples of normal clove oil also gave results in which the absorption and the esterification processes were in accord. Two other samples which were examined showed results in which Thoms's process was in very good agreement with the acetic-pyridine method; whilst Umney's process gave far too high figures—as much as 95 per cent., against 80 per cent. by the other two processes. The figures appear to us most unsatisfactory and unconvincing; but the authors sum up their conclusions as follows:—(1) The esterification-process with acetic anhydride and pyridine serves to determine the eugenol in oil of cloves so long as no other phenol or alcohol is assumed to be present. (2) Umney's method can lead to most erratic conclusions, except when the clove oil is one whose physical characters are quite normal throughout. (3) Thoms's process gives too low results when the oil contains a high amount of nonphenolic constituents.—*Chemist and Druggist*, Dec., 1901, p. 1053.

EXAMINATION OF THE ALBUMINOUS CONSTITUENTS IN URINE.

In a paper in the *Pharmaceutische Post* (1901, p. 753) is given a scheme by Portes and Desmoulieres for the examination of the albuminous constituents in urine, as follows:

Thirty c.c. of well-filtered[1] urine is acidified by adding a few drops of concentrated acetic acid (3 to 4 drops); shake well and allow to stand.

A. Sediment.[2]

a. Soluble in conc. acetic acid (Nucleoalbumin).

Control reaction: Urine + 3 volumes of water is divided into two test-tubes, one of which may serve as a comparison. The one tube upon being acidified with acetic acid becomes perceptibly cloudy, due to a precipitation of the pseudo-mucins.

If a copious precipitate appears it must be collected, washed and dissolved in weak sodium hydrate solution, from which it is again precipitated by adding a saturated solution of magnesium sulphate. In this last precipitate phosphorus will be looked for after calcining with potassium nitrate and soda (by the aid of the nitro-molybdate reaction).

b. Insoluble in concentrated acetic acid (Mucin[3]).

Control reaction: Hydrochloric acid and nitric acid added in small amount precipitates the mucin, which is soluble in an excess of acid solution. Monosodium phosphate also accomplishes the same end. Mucin contains no phosphorus.

B. The solution[4] is treated with 4 drops of trichloracetic acid[5] heated to boiling one-half minute:

I. Precipitate: To 50 c.c. urine (freed from nucleoalbumin and mucin[4] by precipitation in the cold with acetic acid), which should be neutralized[6] and filtered, add a saturated solution of magnesium sulphate.

a. In the warm an insoluble precipitate (Globulin).

---

[1] If the urine contains blood there remains upon the filter the coagulum of fibrin. The urine is strained through linen and the coagulum is washed with water. This coagulum is insoluble in pure water but soluble in sodium fluoride 1 : 100 or in sodium chloride 10 : 100.

[2] In many urines are found precipitates of urates and uric acid which are not floculent but possess a crystalline form readily discernible under the microscope.

[3] According to Leidie the mucin of a decomposed urine which shows an ammoniacal fermentation is also a nucleoalbumin; what has been identified in

Control reaction: It is precipitated by a stream of CO_2 and by a concentrated sodium chloride solution and ammonium sulphate.

b. Solution. When acidified with 2 or 3 drops of acetic acid $\frac{N}{10}$ and boiled, a precipitate is produced.

1. Soluble when a drop of crystallizable acetic acid is added [Albumine (acetosoluble)].

Control reaction: It is thoroughly precipitated by adding ammonium sulphate in excess. Trichloracetic acid precipitates the same out of the acetic acid solution.

2. Insoluble when a drop of glacial acetic acid is added (Serin).

Control reaction: Precipitated by adding ammonium sulphate in excess and by concentrated mineral acids.

II. Solution. The bulk of the precipitate can be separated from the boiled solution by allowing it to cool.

c. Precipitate, soluble in warm alkali which in the cold is insoluble (Albumose).

Control reaction: Will be precipitated by ammonium sulphate in excess. Hydrochloric acid added to the urine gives a precipitate in the cold which disappears upon heating and reappears after cooling. With acetic acid—tannin the albumose is precipitated. The double iodides of potassium and mercury, as well as picric acid, give with the urine a voluminous precipitate soluble upon heating.

D. If a precipitate be present or not, 20 c.c. of the urine are taken, to which is added, with vigorous shaking, crystallized ammonium sulphate to saturation; allow to settle and filter. To the filtrate is added 2 or 3 drops of very dilute copper sulphate solution, after

---

such urines as pyrin is nothing other than an alkaline albuminate, produced by the action of ammonia upon the albuminous material (that is, the pus). An unfermented urine containing pus does not show the characteristics of mucins or pyrins (precipitated with acetic acid).

[4] If the mass of nucleoalbumin or mucin is small, then the addition of acetic acid produces a uniform cloudiness that lasts after the filtration. The precipitation of the flocculi can be hastened by a dilution with one or two volumes of water; after a few hours it is filtered and in this manner a clear fluid is obtained, and in which the other albuminous constituents can be looked for.

[5] The trichloracetic acid also precipitated the alkaloids, yet the precipitate disappeared upon dilution with water, by heating, by adding alcohol, and by an excess of this acid.

[6] It is neutralized with potassium or sodium hydrate until a rose color appears upon the addition of phenolphtalein.

which soda is added in slight excess, producing a violet color (Peptone).

Control reaction: The filtrate from the urine saturated with ammonium sulphate is diluted with equal volumes of water and acetic-acid-tannin, which forms a precipitate.

W. S. WEAKLEY.

THE IDENTIFICATION OF TYPHOID BACILLI.

Hayaschikawa found, *Apoth.-Zeit.*, 1901, p. 734, that by the use of urine gelatine nutrient media,[1] he was able to dintinguish a colony of typhoid bacilli from a colony of the common colon bacilli with which the typhoid bacilli are often mixed, and which are often mistaken one for the other, especially in inexperienced hands. These investigations were carried out with a 3·3 per cent. urine gelatin and the bacilli were grown at a temperature of 22° C. The urine gelatin media must not be too old, the temperature must be uniform, and the colonies must not be planted too closely together to get the characteristic frayed margin of the deeper colonies of these two bacilli.

A discrimination, however, can be made between these two bacilli as follows: First, by the size, for the typhoid colonies in the same stage of development are from one-fourth to one-half times smaller than the colon colonies. Secondly, by the color, for the typhoid colony remains a clear yellow for about forty-five hours, whilst the colon colony appears much darker. Thirdly, by the nature of these thread-like appendages[2] constituting the frayed margin; with the typhoid colonies these threads are much longer, more delicate and more twisted than in the colon colonies in which they appear shorter, more quickly thickened, plaited and are less strongly twisted.

---

[1] Sometimes a crystal formation interferes with this thread-like formation, and, as a remedy, the urates and phosphates should be separated before the urine is added to the gelatin. The writer proceeds as follows: Allow the urates to separate by cooling the fresh and normal urine, filter, make alkaline with a concentrated sodium hydrate solution and allow to stand twenty-four hours to permit the phosphates to separate. The last procedure is not absolutely necessary, as it has been shown that the phosphates do not usually precipitate in a slightly alkaline mixture.

[2] In the usual 3·3 per cent. meat water nutrient gelatin this thread-formation is not so marked.

In the 6 per cent. urine gelatine which melts at 28° the fraying is not as clearly marked as in the 3·3 per cent. The time for the examination of the colonies is between twenty and forty hours. From the fortieth hour, the frayed character becomes obliterated and makes observation difficult. W. S. W.

NEW REMEDIES OF 1901.[1]

Tyratol—See Thymatol.

Tyrosal—Antipyrine-salicylacetate.

Urea Quinate—See Urol.

Uresin—Urotropin-lithium citrate. Solvent for gravel. (Do not confound with urosin-lithium quinate).

Urol—Urea Quinate. Used in gout and gravel (both urinary and renal).

Urosteril—Preparation containing extract of pichi pichi. Antigonorrhoic.

Urotropin-Lithium Citrate—See Uresin.

Uzane—Dental anesthetic.

Vegetaline—A kind of butter prepared from cocoanut.

Vioform—Iodochloroxyquinoline. Succedaneum for iodoform.

Voandzou—*Glycine subterranea.* The seeds are highly nutrient.

Xanol—Sodium-caffeine salicylate. Diuretic.

Xeranthemum Annuum—A Compositæ recommended as a cardiac tonic.

Xylopia Æthiopica—Æthiopian pepper. Macerated fruits are used as an embrocation; the decoction is used in bowel complaints; fruit also anthelmintic and aphrodisiac.

Zomol—Nutrient prepared from meat.

EDITORIAL NOTES AND COMMENTS.

A MEMORIAL TO DR. CHARLES RICE.

In the January issue of this JOURNAL attention was directed to a movement which had for its object the marking of the grave of Dr. Charles Rice with a suitable monument. Since that time a communication has been received from Joseph P. Remington, the Chairman of the Committee of Revision of the U. S. Pharmacopœia, from which the following extract is taken:

---

[1] *Merck's Report*, January, 1902.

"The Board of Trustees and Committee of Revision of the United States Pharmacopœial Convention have inaugurated a movement to erect a monument and prepare a volume containing a portrait, with a sketch of the life and labors of their late beloved Chairman, Dr. Charles Rice. A memorial fund has been started by the committee and an appropriation made. As soon as the movement began, it became evident that the many friends of Dr. Rice throughout the country would be glad to make contributions." . . . "Mr. Samuel A. D. Sheppard, the well-known Treasurer of the American Pharmaceutical Association, has consented to act as chairman of the fund, and he will receive all subscriptions."

It is not necessary to urge this matter unduly, as we believe that it is only necessary for the friends of Dr. Rice to know of this movement in order for them to contribute to the proposed fund.

THE CHEMISTRY OF IONS.

In a summary on the "Dissociating Power of Different Solvents," H. C. Jones (*Amer. Chem. Jour.*, 1901, 249) says:

(1) That with the exception of hydrogen dioxide water is the strongest ionizer. Next to this comes formic acid. Of the more common solvents, methyl alcohol dissociates to a much greater degree than ethyl alcohol. Indeed it is true, in general, that *in an homologous series of solvents the lesser members have the greater dissociating power.*

(2) The dissociating power of a solvent appears to be a function of *all* the physical or chemical properties of a substance and not of any one function.

(3) The results of a great many experiments tend to show the chemical inertness of molecules. Most, if not all, chemical reactions are reactions between ions, and molecules as such do not enter into the reactions at all. As the reactions proceed, and the ions already present are used up, the molecules are gradually dissociated and furnish new ions, which then enter into the reaction. The *chemistry of atoms and molecules has thus given place to the chemistry of ions.*

PENNSYLVANIA HOSPITAL.

The sesqui-centennial, 150th, annual report of the Pennsylvania Hospital shows the hospital to be well equipped for the care of the sick and injured, and its managers devising ways for administering

to those (as those afflicted with senile dementia) who do not seem to have been considered as proper cases for "homes" and hospitals. It is interesting to note that Frederick Fraley, one of Philadelphia's best known public-spirited men, presided at the 150th annual meeting of the contributors. Since that time he has departed this life, having contributed for years his support, presence, and influence to the perpetuation of scientific educational and organized beneficent work in the city of Philadelphia.

HUMAN AND BOVINE TUBERCULOSIS.

In *Pediatrics*, August 15, 1901, appears the following résumé of this subject:

"Koch's views in regard to the non-transmissibility of bovine tuberculosis to man, as set forth in his address delivered before a General Meeting of the British Congress on Tuberculosis, have by this time become pretty generally familiar throughout the lay and medical worlds. He has stated fairly positively what cannot be demonstrated except indirectly. The indirect demonstration, however, he regards as fairly conclusive, as he says: "It is well known that the milk and butter consumed in great cities very often contain large quantities of the bacilli of bovine tuberculosis in a living condition, as the numerous infection experiments with such dairy products on animals have proved. Most of the inhabitants of such cities daily consume such living and perfectly healthy virulent bacilli of bovine tuberculosis, and unintentionally carry out the experiment which we are not at liberty to make. If the bacilli of bovine tuberculosis were able to infect human beings many cases of tuberculosis caused by the consumption of alimenta containing tubercle bacilli could occur among the inhabitants of great cities, especially the children." He holds that tuberculosis can only be assumed with certainty to be caused by alimenta when the intestine suffers first. Only twice does he remember having seen primary tuberculosis of the intestine. He cites statistics to prove how exceedingly rare this affection is, and does not think it at all necessary to have to assume infection by the bacillus of bovine tuberculosis to explain the few cases of primary intestinal tuberculosis that do occur. He also considers that he has conclusively proved by experiment that human tuberculosis cannot be transmitted to animals. These propositions

are not new but have never before been *so positively* enunciated by an authority on this disease.

"In an address before the Canadian Medical Association in August, 1899, Professor Adami called attention to how scanty the evidence was to prove the transmission of animal tuberculosis to man. He also stated that human tubercle bacilli when inoculated into cattle would produce only local and transient effects. In a paper read before the British Medical Association, August, 1899 (*Pediatrics*, Vol. VIII, No. 8, 1899) Dr. George F. Still, after analyzing 269 necropsies on tuberculous children under twelve years of age, concluded that the commonest channel of infection with tuberculosis in childhood is through the lung; that infection through the intestine is less common in infancy than in later childhood; that milk, therefore, is not the usual source of tuberculosis in childhood, perhaps due to precautions taken in boiling and sterilizing; that inhalation is the commonest mode of infection in the tuberculosis of childhood and especially infancy, etc. So it is evident that medical thought has been tending in this direction for some time. This is a subject of vast import and nowhere can the adage '*festina lente*' be more fittingly applied."

On the other hand, in the introduction to his admirable paper on the "Relation of Bovine Tuberculosis to Public Health," Salmon, the chief of the Bureau of Animal Industry, says:

"In treating of the communication of tuberculosis from cattle to man, it is first shown that the statement that human tuberculosis is not communicable to cattle is unwarranted by the evidence, since both Martin in England, and Chauveau in France have obtained positive infection and extensive disease by feeding to cattle tubercular material from human sources. It is further shown that the human and bovine diseases cannot be entirely different, because tuberculin produced from human bacilli causes reaction in bovine tuberculosis. Another argument used in this connection is that the whole list of diseases which affect a wide range of animal life, being communicable between widely separated species of animals, there is no other disease which is not also communicable to man. The inference is, therefore, that as bovine tuberculosis is communicable to a large number of species and to widely separated forms of animal life, it is also communicable to man.

"As more direct evidence, there are cited cases to establish—

"(1) The accidental infection of man by inoculation with bovine bacilli.

"(2) The infection of man by consuming the milk of tuberculous cows.

"To corroborate this evidence statistics are presented proving the occurrence with mankind of a large number of cases of intestinal and other abdominal forms of tuberculosis, particularly in England and Scotland. It is shown that there is no relation between the total number of cases of tuberculosis and the cases of abdominal tuberculosis in various countries, and the conclusion is drawn that the primary abdominal tuberculosis probably is not caused entirely by infection from other causes of human tuberculosis. It is also shown from statistics of postmortem examinations carefully made by competent persons that in some parts of the world at least there is a considerable proportion of cases of tuberculosis in man in which the infection occurred through the intestine.

"These lines of evidence are clearly opposed to the principal assertion made in the paper read by Koch at the British Congress on Tuberculosis this year. But this is not the worst aspect of the case, since the evidence of Delepine and Still indicates that there are many more cases of intestinal tuberculosis in children than are actually discovered or recognized. More than this, it is shown on the evidence of such competent witnesses as Woodhead, St. Clair Thompson, and Lord Lister that infection through the medium of the food may not necessarily be accompanied by disease of the intestines. The organs first attacked after feeding on tubercular material may be the mesenteric glands and liver, or even the bronchial and mediastinal glands and the lungs. While, therefore, the facts show that the intestines are sometimes the first organs attacked after tubercular infection is taken into the digestive organs through the mouth, they also show that the number of cases of primary intestinal infection is no indication of the number of cases in which the infection has been carried by the food."

In commenting upon the above, the editors of the Bulletin issued by the Delaware State Board of Health say: "In our praiseworthy agitation of a pure milk law we must not forget that milk may contain substances far more destructive to life than the usual adulterations. Even formaldehyd sinks into insignificance when compared with tubercle bacilli and pus-forming organisms."

REVIEWS AND BIBLIOGRAPHICAL NOTICES.

A very timely "Treatise on Smallpox" is announced for publication early in April by J. B. Lippincott Company. It is written by Dr. George Henry Fox, Professor of Dermatology in the College of Physicians and Surgeons, New York City, with the collaboration of Drs. S. Dana Hubbard, Sigmund Pollitzer, and John H. Huddleston, all of whom are officials of the Health Department of New York City, and have had unusual opportunities for the study and treatment of this disease during the present epidemic.

The work is to be in atlas form, similar to Fox's "Photographic Atlas of Skin Diseases," published by the same house. A strong feature of the work will be its illustrations, reproduced from recent photographs, the major portion of which will be so colored as to give a very faithful representation of typical cases of variola in the successive stages of the disease; also unusual phases of variola, vaccinia, varicella, and diseases with which smallpox is liable to be confounded. These illustrations number thirty-seven and will be grouped into ten colored plates, 9½x10¼ inches, and six black-and-white photographic plates.

The names of Dr. Fox and his associates assure the excellence of the work, in which will be described the symptoms, course of the disease, characteristic points of diagnosis, and most approved methods of treatment.

PHARMACEUTICAL MEETING.

The fifth of the series of pharmaceutical meetings of the Philadelphia College of Pharmacy, for 1901–1902 was held on Tuesday, February 18th. Mr. James T. Shinn, Treasurer of the College, presided.

The first speaker was Prof. Edgar F. Smith, Professor of Chemistry and Vice-Provost of the University of Pennsylvania, who read a valuable paper on "The Basis of Atomic Weights." He reviewed the work of Dalton, the philosopher, and of Berzelius, the eminent experimenter, who enriched science in every field he investigated. The former is known chiefly because he promulgated the doctrine that the weight of the hydrogen atom equals 1. Berzelius developed methods of research, and he chose oxygen as a standard for

comparison, as most elements form oxides or compounds with oxygen.

Professor Smith referred to some of the difficulties in determining atomic weights, and illustrated the same with the work which he and his students have been carrying on for a number of years in the Harrison Chemical Laboratory, particularly on palladium and tungsten.

Berzelius gave the value of 100 to oxygen, but this is no longer retained. Three systems have been used in calculating the molecular weights of organic compounds: (1) H = 1; C = 12; O = 16: (2) H = 1·008; C = 12; O = 16: (3) H = 1; C = 11·91; O = 15·88. The speaker showed in a few instances what great differences would result in the calculation of the molecular weights of oxalic acid, or the sugar $C_{12}H_{22}O_{11}$ with the three systems. Furthermore, inasmuch as the great work of Beilstein, in which over 70,000 organic compounds are described, is based on the first of these systems, it would mean a recalculation of all these compounds, for, as Morley has shown, if H = 1, then oxygen equals 15·88, and if oxygen equals 16, then hydrogen equals 1·008.

Professor Smith referred to the labors of the committee of the German Chemical Society, and compared the international and didactic tables published by them. He then gave some of the arguments in favor of the standard that hydrogen equals 1 as follows: (1) It is the original Daltonian standard; (2) it is the most natural basis, because hydrogen is the lightest atom known and is the standard for determining the densities of gases and valence; (3) if oxygen is made the standard, then all vapor densities must be changed; (4) with the physicist hydrogen is the standard; (5) hydrogen has a uniform rate of expansion; (6) the difficulty of teaching that H = 1·008.

The following are some of the features in favor of the standard oxygen equals 16·00: (1) Few elements can be compared directly with hydrogen, of all the elements known, but seven or eight have had their atomic weights compared directly with oxygen; (2) with oxygen as the standard the atomic weights of a very large number of the elements are whole numbers, as is seen in a comparison of the international (O = 16·00), and the didactic (H = 1) tables; (3) this is of very material importance in making calculations in quantitative analysis; and (4) must be less burdensome to the memory;

(5) all the organic compounds given in Beilstein are based on the standard O = 16; (6) all the actual workers in making atomic weight determinations prefer oxygen as the basis. Professor Smith referred to the fact that other elements had been proposed as the standard for comparison, viz., carbon, silver and iodine, but stated that oxygen had met the demands for comparison. He also stated that it is possible that if carbon were taken as the standard that it would meet the various objections of the adherents of the two other standards. In conclusion, Professor Smith said that one writer claimed that if we accept hydrogen as the standard, then we must put ourselves back one century and must wait fifty years to be where we are to-day.

The paper was discussed by Professors Remington and Sadtler, Mr. Shinn and Mr. Wilbert. The latter suggested that inasmuch as all the continental countries had adopted the standard oxygen equals 16, that it would be well if the U.S.P. could do likewise.

The next paper was on "Adulteration of Drugs and Foods," by Dr. Albert Robin, Delaware State Board of Health. The paper was discussed by Messrs. Boring, Lowe, Shinn, Miller, Poley and others. Dr. Miller alluded to the fact that Americans are not the only people who are gullible in the respect of taking patent medicines, but that these are sold extensively in all the principal cities of Europe which he had visited recently. Mr. Poley spoke of the inconsistency of people taking the labels on patent medicines, for gospel, when they would not accept the check of a man unless they knew something of his character or standing.

The last paper was by Mr. Wilbert on "Dose Measures and Measured Doses." (See page 120). The paper was discussed by Messrs. Lowe, Boring, Wiegand, Shinn, and others.

In answer to Dr. Lowe's remarks on the methods of engraving graduates, Mr. Wilbert said: It must be remembered that medicine glasses are not graduated with the same care. As indicated in the paper, medicine-glasses are, as a rule, graduated correctly at but one point, and the intervening graduations are filled in usually according to rule of thumb. This point is well illustrated by tables 2 and 3 of the paper. Medicine-glasses that are graduated by means of a block pattern occasionally suffer from the same cause; in one lot that Mr. Wilbert had seen, the measure was evidently measured at the teaspoonful quantity, and the block sub-

sequently divided for the teaspoonful quantities with little or no regard for the actual capacity of the glass.

Mr. Wilbert called particular attention to the fact that all of these glasses are absolutely unreliable, for one reason or another, for measuring teaspoonful quantities of medicine containing active or poisonous ingredients.

The variation of spoons is due largely to the fact that a comparatively large quantity of liquid may be heaped up on a full spoon; for instance, a teaspoon that, when filled to the brim, holds but 5 c.c., will, when heaped with a liquid having the viscosity of water, readily hold 8 c.c.; the dessertspoon can be made to hold nearly 14 c.c. and the tablespoon nearly 19 c.c.

While drops are admittedly uncertain quantities, it is possible to have a dropper that will be much more accurate and reliable than the proposed standard dropper now before the Pharmacopœial Revision Committee. In reference to minim measures, would it not be more in keeping with pharmaceutical standards, he said, if we should advocate a measure graduated in the metric system. Personally, he thinks that any factor that would advance the introduction or use of the metric system would be of advantage.

Mr. Wiegand alluded to another form of graduate measure which commends itself to the careful pharmacist when dispensing active remedies, viz., the measure shaped like a Theban vase and prolonged at the upper end into a narrow neck, upon which the capacity is marked. This avoids the variation which a wide surface renders almost inevitable in rapid work.

The following provisional program has been arranged for the next meeting on Tuesday, March 18th:

Liquid Soaps for Surgical and Toilet Purposes. By M. I. Wilbert, Apothecary at the German Hospital, Philadelphia.

Deodorized Opium Preparations. By Albert E. Ebert, Chicago.

The Spread of Tuberculosis by Coughing. By Dr. L. Napoleon, Boston.

Ricin Soap. By Frederick T. Gordon. H. K.